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Applicant : THE RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK

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For : SYSTEM AND METHOD FOR TOMOGRAPHIC IMAGING OF DYNAMIC PROPERTIES OF A SCATTERING MEDIUM

Commissioner for Patents
Box PCT
Washington, D.C. 20231

Attention: IPEA

AMENDMENT UNDER ARTICLE 34

Sir:

The International preliminary Examination Authority is requested to amend the description and claims of the above identified International Application prior to examination based on the enclosed Substitute Sheets: 5, 9, 15-16, and 18-41.

The status of the **description** is as follows:

1) The following original pages are unchanged: 1-4, 6-8, 10-14, 17, 20, and 23-25.

2) The following original pages are amended:

p.5, line 15, delete "photograph" and insert--schematic illustration-- in its place.

p.9, line 14, delete "spatial temporal and insert --spatiotemporal-- in its place.

p. 15, line 18 insert--about-- before "1 mm. diameter".

p.16, line 21, delete "of".

p. 18, line 12-13, delete "a receiver or detector fiber bundle."

p.22, line 1 delete "thereby" after "thereby".

p.22, line 23, move "The implementation in FIG 9 illustrates one use of a silicon photo-diode in process 904, which can be replaced by various detectors previously mentioned." to p. 23, line 19 after "Real time measurement".

p.26, line 7 delete "lectronic" and insert --electronic-- in its place.

The status of the **claims** is as follows:

1) Claims 1-14, 16-21, and 23-54 are unchanged.

2) Claims 55-61 are new.

3) Claims 15 and 22 are amended.

No new matter has been added. Support for these amendments can be found throughout the description and drawings, especially at page 6, lines 17-21 and page 9 line 21.

Respectfully submitted,

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p. 18, line 13, add--FIG. 6 indicates 2D imaging planes formed by multiple source/detector positions along a line that can be used with this particular pattern. The labels refer to the numbers of sources/detectors found along those lines of optical fiber ends on the pad using the following nomenclature: "S" followed by a number indicates the number of source positions along that line; "D" followed by a number indicates the number of detection points along that line. For instance, "S3-D3" indicates an imaging plane formed by three source positions and three detection points.-- before "Basically, the design allows for".

p. 19, line 18, add --The folding structure can be extended to accommodate a more "tear drop" or "bullet" shape of the target medium by attaching additional circular iris-like structures on top that expand and contract with the hemisphere. FIG. 7 shows the combination of the hemisphere with one top iris comprising receptacles for 8 additional fiber bundles leading to an overall number of 25 source by 25 detector positions at the main vertices for this configuration. More than one iris can be attached to the top of the hemisphere. The diameter of the additional top irises may or may not differ from the hemisphere diameter. The detectors or energy receivers may be disposed about the imaging head and the detectors are located on the inner aspect of the expanding imaging head. Additional fiber bundles can be attached to the interlocking joints, permitting up to a 49 source by 49 detector measurement for the hemisphere only and up to 16 source/detector positions per added iris.-- after "seventeen (17) detector measurement." and delete "Additional fiber bundles can be attached to the interlocking joints, permitting up to a 49 source by 49 detector measurement." on lines 21-22.

p.21, line 19, delete "(PTA = Programmable Transimpedance Amplifier)" and on page 21, line 18 after "803" insert --(PTA = Programmable Transimpedance Amplifier)--.

p. 21, line 21 insert --804-- after "(PGA)".

BRIEF DESCRIPTION OF THE FIGURES

For a better understanding of the invention, together with the various features and advantages thereof, reference should be made to the following detailed description of the preferred embodiments and to the accompanying drawings wherein:

FIG. 1 is a block diagram of one embodiment of a system according to the invention;

FIG. 2 is a block diagram illustrating one implementation of the system in FIG. 1;

FIG. 3 is a perspective view of a servo-motor apparatus useful in this invention to illuminate a number of fiber bundles with a single energy source;

FIG. 4 is a schematic illustration of the disposition for examining human tissue such as a human breast;

FIG. 5 is a schematic illustration of a planar imaging head useful in one embodiment of the invention;

FIG. 6 is one embodiment for the source detector arrangement on the imaging head shown in FIG. 5;

FIG. 7 is an illustration of a spherical imaging head useful in practicing the invention;

FIG. 8 is a block diagram of a detector channel useful in practicing the invention;

FIG. 9 is a graphical representation of one implementation of a timing scheme used in the system of FIG.1;

FIG. 10 is a diagram illustrating the sequence of certain events in a multiple channel embodiment of the invention;

displaying the raw data in a color mapping format, features can be extracted by sole visual inspection. In addition to that, analysis algorithms of various types such as, but not limited to, linear and non-linear time-series analysis or pattern recognition methods can be applied to the series of raw data. The advantage of using these analytical methods is the improved capability to reveal dynamic signatures in the signals.

In another implementation, image reconstruction methods may be applied to the sets of raw data thereby providing time series of cross-sectional images of the scattering medium. For these implementations, analysis methods of various types such as, but not limited to, linear and non-linear time-series analysis, filtering, or pattern recognition methods can be applied. The advantage of using such analysis is the improved extraction of dynamic features and cross-sectional view, thereby increasing diagnostic sensitivity and specificity. These methods are explained in detail in the '355 and '322 patents, which were previously described and incorporated in as reference.

The invention reveals measurements of real-time spatiotemporal dynamics. Depending on the implementation, an image of dynamic optical properties of scattering medium such as, but not limited to, the vasculature of the human body in a cross-sectional view is provided. The technology employs low cost, compact instrumentation that uses non-damaging near infrared optical sources and features several alternate imaging heads to permit investigation of a broad range of anatomical sites.

In another implementation, the principles of the present invention can be used in conjunction with contrast agents such as absorbing and fluorescent agents. In another variant, the present invention allows the cross-sectional measurements of changes in

motion protocols such as in a start-stop fashion where the motor stops at a desired location thereby allowing the stable coupling of light into a transmitting fiber bundle. After the measurement at this source location is performed, the motor moves on to the next transmitting fiber. Motion control is in two-way communication with the timing control **104** thereby allowing precise timing of this procedure. Motion control allows the assignment of relative and/or absolute mirror positions allowing for precise alignment of the mirror with respect to the physical location of the fiber bundle. The mirror **306** is surrounded by a cylindrical shroud **309** in order to shield off stray light to prevent cross-talk. The shroud comprises an aperture **310** through which the light beam **302** passes toward the transmitting fiber. It is recognized and incorporated herein other schemes which may be used,(e.g., use of a fiber-optic switching device) to sequentially couple light into the transmitting fibers.

In an equivalent embodiment, fast switching of source positions is accomplished by using a number of light sources, each coupled into one of the transmitting fibers **306** which can be turned on and of each independently by electronic means.

The device employs the servo-motor control system **308** in FIG. 3 with beam steering optics, described above, to sequentially direct optical energy emerging from the source optics onto about 1 mm diameter optical fiber bundles **306**, which are mounted in a circular array in the multiplexing input coupler **300**. The transmitting optical fiber bundles **306**, which are typically 2-3 meters in length are arranged in the form of an umbilical and terminate in the imaging head **206**.

Depending on the implementation, the apparatus of the present invention required for time-series imaging, employs the value of using a geometrically adaptive measurement head or imaging head. The imaging head of the present invention provides features that include, but are not limited to, 1) accommodating different size targets (e.g., breast); 2) stabilizing the target against motion artifacts; 3) conforming the target to well-defined geometry; and 4) to provide exact knowledge of locations for sources and detectors. Stability and a known geometry both contribute to the use of efficient numerical analysis schemes.

There are several different embodiments of the imaging head for data collection that may utilize the principles of the present invention. For example the use of an iris imaging head previously disclosed in the '322 and '355 patents , which are incorporated by reference in this disclosure, may be used with the principles of the present invention.

Described below are two exemplary imaging heads with the understanding that the invention may or may not use any type of imaging head, and if an imaging head is used, it would provide the features previously described.

As illustrated in FIG. 4, the iris unit can be employed as a parallel array of irises **402**, **404**, **406** enabling volume imaging studies. FIG. 4 illustrates how this can be configured for studying a medium **410**, in this example a human breast, using an imaging head **408**. As described previously, the medium used in the present invention can be any medium, which allows scattering of energy.

In one implementation, the imaging head illustrated in FIG. 5 is a flexible pad configuration. This planar imaging unit functions as a deformable array and is well suited to investigate body structures too large to permit transmission measurements (e.g.,

mm in diameter. Depending on the implementation, eighteen (18) of the sixty-three (63) fiber bundles may be arranged in an array to serve as both optical energy sources or energy transmitters, and receivers to sequentially deliver light to a designated target and receive emerging optical energy. In this implementation, the remaining forty-five (45) fiber bundles act only as receivers of the emerging optical energy.

The geometry of the illumination array is not arbitrary. The design shown in Figure 6 as an exemplary illustration has been configured, as have other implementations, to minimize the subsequent numerical effort required for data analysis while maximizing the source-density covered by the array. The fiber bundles are arranged in an alternating pattern as described by FIG. 6 and shown here with the symbols "X" and "0". In one implementation, a pattern of 00X000X00, X000X000X can be used on the imaging head. 'X' denotes a source/receiver fiber bundle, and '0' is a receiver only. FIG. 6 indicates 2D imaging planes formed by multiple source/detector positions along a line that can be used with this particular pattern. The labels refer to the numbers of sources/detectors found along those lines of optical fiber ends on the pad using the following nomenclature: "S" followed by a number indicates the number of source positions along that line; "D" followed by a number indicates the number of detection points along that line. For instance, "S3-D3" indicates an imaging plane formed by three source positions and three detection points. Basically, the design allows for the independent solution of two dimensional (2-D) image recovery problems from an eighteen (18) point source measurement. As a result, a composite three dimensional (3-D) image can be computed from superposition of the array of 2-D images oriented perpendicular to the target

surface. Another advantage of this geometry is that it readily permits the use of parallel computational strategies without having to consider the entire volume under examination.

The advantage of this geometry is that each reconstruction data set is derived from a single linear array of source-detector fibers, thereby enabling solution of a 2-D problem without imposing undue physical approximations. The number of source-detector fibers belonging to an array can be varied. Scan speeds attainable with the 2-D array illustrated in FIG 6 are the same as for other imaging heads with 2-D arrays since the scan speed depends only on the properties of the input coupler. Thus, faster scan speed are available for the creation of a 3-D image.

In another implementation, illustrated in FIG. 7, is an imaging head based on a "Hoberman" sphere geometry. In a Hoberman structure, the geometry is based on the intersection of a cube and an octahedron, which makes a folding polyhedron called a trapezoidal icosatetrahedron. This structure has been modified and implemented in a form of an imaging head of a hemispherical geometry. For many purposes of the instant invention, it is appropriate to use design features of smoothly varying surfaces based on the Hoberman concept of expanding structures. Depending on the implementation, other polygonal or spherical-type shapes may also be used with the principles of the present invention for other imaging head designs. Adjustment of the device in Figure 7 causes uniform expansion or contraction, thereby always preserving a hemispherical geometry. Imaging head **700** illustrates one example of modification to the "Hoberman" geometry. A receptacle for the fiber bundles **701** is disposed about imaging head **700**. Target volume **702** is where the medium would enter the imaging head in this implementation. This geometry is well suited for the investigation of certain tissues such as the female

breast or the head. Depending on the implementation, attachment of optical fibers to the vertices of the hemisphere allows for up a seventeen (17) source by seventeen (17) detector measurement. The folding structure can be extended to accommodate a more "tear drop" or "bullet" shape of the target medium by attaching additional circular iris-like structures on top that expand and contract with the hemisphere. FIG. 7 shows the combination of the hemisphere with one top iris comprising receptacles for 8 additional fiber bundles leading to an overall number of 25 source by 25 detector positions at the main vertices for this configuration. More than one iris can be attached to the top of the hemisphere. The diameter of the additional top irises may or may not differ from the hemisphere diameter. The detectors or energy receivers may be disposed about the imaging head and the detectors are located on the inner aspect of the expanding imaging head. Additional fiber bundles can be attached to the interlocking joints, permitting up to a 49 source by 49 detector measurement for the hemisphere only and up to 16 source/detector positions per added iris.

Depending on the implementation, light collected from the target medium is measured by using any of a number of optical detection schemes. One embodiment uses a fiber-taper, which is bonded to a charged coupled detector (CCD) array. The front end of the fiber taper serves to receive light exiting from the collection fibers. These fibers are preferably optical fibers, but can be any means that allows the transmission and reception of signals. The back end of the fiber taper is bonded to a 2-D charge-coupled-detector (CCD) array. In practice, use of this approach generally will require an additional signal attenuation module.

An alternate detection scheme employs an array of discrete photo detectors, one for each fiber bundle. This unit can be operated in a phase lock mode thereby allowing for improved rejection of ambient light signals and the discrimination of multiple simultaneously operated energy sources.

In another embodiment, in order to fulfill the demands posed by the desired physiological studies on the instrument, the following features characterize the detector system: scalable multi-channel design (up to 32 detector channels per unit); high detection sensitivity (below 10 pW); large dynamic range ($1:10^6$ minimum); multi-wavelength operation; ambient light immunity; and fast data acquisition (order of 100 Hz all-channel simultaneous capture rate).

To achieve this, the detector system uses photodiodes and a signal recovering technique involving electronic gain switching and phase sensitive detection (lock-in amplification) for each detector fiber (in the following referred to as detection or detector channels) to ensure a large dynamic range at the desired data acquisition rate. The phase sensitive signal recovery scheme not only suppresses electronic noise to a desired level but also eliminates disturbances given by background light and allows simultaneous use of more than one energy source. Separation of signals from simultaneously operating sources can be achieved, as long as the different signals are encoded in sufficiently separated modulation frequencies. Since noise reduction techniques are based on the reduction of detection bandwidth, the system is designed to maintain the desired rate of measurements. In order to achieve a timing scheme that allows simultaneous readout of the channels, a sample-and-hold circuit (S/H) is used for each detection channel output. The analog signals provided by the detector channels are sampled, digitized and stored

using the data acquisition system **116**. One aspect is the flexibility and scalability of the detection instrument. Not only are the detector channels organized in single, identical modules, but also the phase detection stages, each containing two lock-in amplifiers, are added as cards. In this way, an existing setup can easily be upgraded in either the number of detector channels and/or the number of wavelengths used (up to four) by cloning parts of the existing hardware.

FIG. 8 shows the block diagram of one implementation of a detector channel. In this implementation , two energy sources are being used. After detecting the light at the optical input **801** by a photo detector **802** the signal is fed to a transimpedance amplifier **803**.(PTA=Programmable Transimpedance Amplifier) The transimpedance value of **803** is externally settable by means of digital signals **813**. This allows the adaptation to various signal levels thereby increasing the dynamic range of the detector channel. The signal is subsequently amplified by a Programmable Gain Amplifier (PGA) **804** whose gain can be set externally by means of digital signals **814**. This allows for additional gain for the lowest signal levels (e.g., in one implementation ~pW-nW) thereby increasing the dynamic range of the detector channel.

In one embodiment, at least one energy source is used and the signal is sent to at least one of lock-in amplifiers (LIA) **805, 809**. Each lock-in amplifier comprises an input **808,812** for the reference signal generated by phase shifter **204** from FIG 2. After lock-in detection, the demodulated signal is appropriately boosted in gain by means of a programmable gain amplifier (PGA) **806, 810** in order to maximize noise immunity during further signal transmission and to improve digital resolution when being digitized. The gain of PGA **806, 810** is set by digital signals **815**.

At each output, a sample-and-hold circuit (S/H) **807, 811** is used for freezing the signal under digital timing by means of signal **816** for purposes described herein.

In one embodiment, the signal **815** is sent to **806, 810** in parallel. In one embodiment, the signal **816** is sent to **807, 811** in parallel.

As previously illustrated in FIG. 1, the analog signal provided by each of the channel outputs is sampled a data acquisition system **116**. In one embodiment, PC extension boards might be used for this purpose. PC extension boards also provide the digital outputs that control the timing of functions such as gain settings and sample-and-hold.

As previously noted, timing is crucial in order to provide the desired image capture rate and to avoid false readings due to detector-to-detector time skew. FIG. 9 shows one improvement of the invention over other timing schemes. With systems not comprising fast adaptable gain settings (such as some CCD based systems), a schedule according to **905** has to be implemented. A time series of data is acquired for a fixed source position. After finishing this task, the source is being moved **902** with respect to the target **901** and another series of data is being collected. Measurements are being performed in this fashion for all source positions. Every image **903** of the resulting time series of reconstructed images are being reconstructed from data sets merged together from the data for each source position. This schedule does not allow real-time capture of all physiologic processes in the medium and therefore only applies to certain modes of investigation. Although we are aware of the use of such schemes, e.g., when monitoring responses on repeatable maneuvers, the timing scheme for the invention very much improves on this situation.

Because the invention allows for fast source switching and large dynamic range and high data acquisition rates, a schedule indicated by **904** is performed. Here, the source position is switched fast compared to the dynamic features of interest and instantaneous multi-channel detection is performed at each source position. Images **903** are then reconstructed from data sets, which represent an instant state of the dynamic properties of the medium. Only one time series of full data sets (i.e., all source positions and all detector positions) is being recorded. Real time measurement of fast dynamics (e.g., faster 1 Hz) of the medium is provided by the invention. The implementation in FIG 9 illustrates one use of a silicon photo-diode in process **904**, which can be replaced by various detectors previously mentioned.

FIG 10 shows one embodiment of a detailed schedule and sequence of the system tasks **1001** involved in collecting data at a source position and the proceeding of this process in time **1002**. Task **1003** is the setting of the optical de-multiplexer to a destined source position and setting the detectors to the appropriate gain settings. The source position is illuminated for a period of time **1004**, during which the lock-in amplifiers settle **1005**. After the time it takes the S/H to sample the signal **1006**, the signal is being hold for a period of time **1007**, during which all channels are being read pout by the data acquisition. It is worthwhile noticing that during reading out the S/H, other tasks, like moving the optical source, setting the detector gains for the new source position, and settling of the lock-in, are being scheduled. This increases greatly the achievable data acquisition rate of the instrument.

This concept of a modular system is further illustrated in FIG. 11. Up to thirty-two (32) detector modules **1100** (each with 2 lock-in modules each for two modulation

frequencies) are arranged using an enclosure **1102**. The cabinet also can carry up to two phase shifting modules **1104, 1106**, each containing two digital phase shifter under computer control. The ability to adjust the reference phase with respect to the signal becomes necessary since unavoidable phase shifts in the signal may lead to non-optimum lock-in detection or can even result in a vanishing output signal. Organization of data, power supply and signal lines is provided by means of two back planes **1108, 1110**

Depending on the implementation, the detector system design illustrated in FIG. 8 allows one cabinet to operate at a capacity of 32 detectors with four different sources requiring 128 analog to digital circuit (ADC)-board input channels. The upper **1108** and the lower **1110** back plane are of identical layout and have to be linked in order to provide the appropriate distribution of supply-, control- and signal voltages. This is achieved using a 6U-module fitting both planes from the backside, that provides the necessary electric linking paths, and interfaces for control- and signal lines.

FIG. 12 shows the schematic of one implementation of a channel module. In this implementation, a silicon photodiode 1206 is used as the photo-detector. A Programmable Transimpedance Amplifier (PTA) **1201** is formed by an operational amplifier **1204** , resistors **1201** and **1202** and an electronic switch **1205**, the latter of which is realized using a miniature relay. Other forms of electronic switches such as analog switches might be used. Relay **1205** is used to connect or disconnect 1203 from the circuit thereby changing the transimpedance value of **1201**. A high-pass filter (R2, C5) is used to AC-couple the subsequent programmable gain instrumentation amplifier **IC2** (Burr Brown PGA202) in order to remove DC offset. The board-to-board connectors

for the two lock-in-modules are labeled as “slot A” **1210** and “slot B” **1212**. The main connector to the backplane is a 96-pole DIN plug **1220**.

FIG. 13, illustrates the electric circuit of the lock in modules **1210, 1212**. The signal is subdivided and passed to two identical lock-in-amplifiers, each of which gets one particular reference signal according to the sources used in the experiment. The signal is first buffered **IC1, IC7** (AD LF111) and then demodulated using an AD630 double-balanced mixer **IC2, IC8**.

In order to remove undesired AC components, the demodulated signal passes through an active 4-pole Bessel-type filter **IC3, IC4, IC 9, IC10** (Burr Brown UAF42). A Bessel-type filter has been chosen in order to provide fastest settling of the lock-in amplifier for a given bandwidth. Since a Bessel-filter shows only slow stopband-transition, a 4-pole filter is being used to guarantee sufficient suppression of cross talk between signals generated by different sources (i.e. of different modulation frequency). The filter has its 3 dB point at 140 Hz, resulting in 6 ms settling time for a step response (<1% deviation of actual value). The isolation of frequencies separated by 1 kHz is 54 dB. The filters are followed by a programmable gain amplifier **IC5, IC 11**, whose general function has been described above. The last stage is formed by a sample-and-hold chip (S/H) **IC6, IC12** (National LF398).

In another implementation, the phase sensitive detection can be achieved with digital methods using digital signal processing (DSP) components and algorithms. The advantage of using DSP with the principles of the present invention is improved electronic performance and enhanced system flexibility.

In another implementation, an analog-to-digital converter is used for each detector channel thereby improving noise immunity of the signals.

Although illustrative embodiments have been described herein in detail, those skilled in the art will appreciate that variations may be made without departing from the spirit and scope of this invention. Moreover, unless otherwise specifically stated, the terms and expressions used herein are terms of description and not terms of limitation, and are not intended to exclude any equivalents of the system and methods set forth in the following claims.